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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,759	12/08/2003	David John King	CARP0007-101	4275

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,759	KING ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are pending and are under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 are indefinite for reciting "optionally" because it is not clear as to what the exact meaning of the term "optional" is. What options are encompassed by the term as recited in the claims. Further, it is not clear as to what the applicant means by the phrase "optionally substituted", because it is confusing as to if it is intended to modify the term straight, or branched chains.

Claims 4 and 5 are indefinite for reciting "derivatives thereof". The claims are indefinite for reciting "derivative" as the exact meaning of the word in not known. The term "derivative" is not one which has a universally accepted meaning in the art not is it one which has been adequately defined in the specification. The primary deficiency is the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear hw the molecules are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person in the skill in the art to ascribe a discrete and identifiable class of compounds to said phrase.

Claim 5 is unclear because it is unclear if in claim 5 the phrase "polymer" is modifying the term methoxy(polyethylene glycol) and derivatives thereof, or just derivatives thereof. Accordingly, it is impossible to determine the meets and bounds of the claimed invention.

Claim 6 is indefinite for reciting "associated" for it is not known what is meant by the term. Is the term intended to mean the Vh and VL dimers are in the same test tube, aggregated, or dimerized by ionic or hydrogen bonds? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim 7 is indefinite for reciting "and/or" for it is not clear what is meant by the term. Is the term intended to mean that the Vh and the Vh domain is attached to the C-terminal amino acid or does the term mean the Vh or the VL domain is attached to the C-terminal amino acid. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antigen binding antibody fragments, Fab and Fab', does not reasonably provide enablement for just any antibody fragments. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly to "antibody fragment" of antibodies. The specification discloses "antibody fragment" as "antibody fragments of the invention will in general be capable of selectively binding to an antigen" (see page 4 lines 6-7). The specification is silent as to what structural features are necessary for antibody fragments selectively binding to the antigen:

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make derivatives of the claimed antibodies commensurate in scope with the claims, since the specification gives insufficient guidance on or exemplification of how to make all of these types of modified proteins. Antibody fragments, as broadly drawn, read on antibodies that have been subjected to deletions, truncations as well as substitutions. However, applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartż et al. Proc Natl Acad Sci USA Vol. 1987; 84:6408-6411).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art.

In addition, Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979) teach that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function. Rudikoff et al. also teach that the alteration phosphocholine-binding function of a single amino acid in the CDR of a myeloma protein resulted in the loss of antigen-

binding (please see the entire document, in particular)

Further, Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims, insufficient teachings and guidance in the specification, and insufficient working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed using any

antibody fragment.

Removing the term "antibody fragment" or defining precisely what is meant by the limitation in a manner fully supported by the specification that is limiting claims to antigen binding fragments, Fab, Fab' may be sufficient to obviate this rejection.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-4 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Pedley et al (Br. J. Cancer. 1994. 70:1126-1130; IDS – 12/13/2004).

The instant claims are drawn to a modified monovalent antibody fragment comprising a monovalent antibody fragment and at least one polymer molecule in covalent linkage characterised in that each cysteine residue located in the antibody fragment outside of the variable region domain of the fragment is either covalently linked through its sulphur atom to a polymer molecule or is in disulphide linkage with a

second cysteine residue located in the fragment provided that at least one of said cysteine residues is linked to a polymer molecule, an antibody fragment according to claim 1 which is covalently linked to one, two or three polymer molecules through one, two or three cysteine residues located in the fragment outside of its variable region domain, an antibody fragment according to claim 1 or claim 2 wherein the polymer is an optionally substituted straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer or a branched or unbranched polysaccharide, an antibody fragment according to claim 3 wherein the polymer is an optionally substituted straight or branched chain poly(ethylene glycol), poly(propylene glycol) or poly(vinyl alcohol) and derivatives thereof, an antibody fragment according to any one of claim 1 to claim 5 in which the variable region domain is monomeric and comprises an immunoglobulin heavy (V.sub.H) or light (V.sub.L) chain variable domain, or is dimeric and contains V.sub.H-V.sub.H, V.sub.H-V.sub.L or V.sub.L-V.sub.L dimers in which the V.sub.H and V.sub.L chains are non-covalently associated or covalently coupled, an antibody fragment according to claim 6 wherein each V.sub.H and/or V.sub.L domain is covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof, an antibody fragment according to claim 7 which is a Fab or Fab' fragment, further an antibody fragment according to any one of claim 1 to claim 8 covalently attached to one or more effector or reporter molecules, in addition to a pharmaceutical composition comprising a monovalent antibody fragment according to any of the preceding claims together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Pedley et al teach the covalent attachment of polytethylene glycol) (PEG) to an antibody, a Fab fragment, and a Fab' fragment of anti-CEA (see abstract). Pedley modified the cysteine residues outside the variable region of the antibody fragments with PEG producing two polymer molecules per antibody (see page 1128, right side first paragraph). Pedley et al also teach the radiolabelling of the PEG-modified antibodies (see page 1127, left column, Radiolabelling) and the P/G-modified antibody fragment in PBS (see page 1127 left column first Pedley et al modified 111 paragraph). Since claim 5 recites the polymer is methoxytpolyethylene glycol) and derivatives thereof, the claim is being interpreted as reading on polytethylene glycol). The phrase pharmaceutical composition" is given no weight because it is being interpreted as an intended use of the product. Thus, the reference of Pedley et al meets the limitations of the claims.

Hence, the instant claims are rejected under 35 U.S.C. 102(b) as being anticipated by Pedley et al.

6. Claims 1, 9 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated Griffiths et al (U.S. Patent 5,670,132, Date Filed: 09/20/1994; IDS – 12/13/2004).

The instant claims have been described supra.

Griffiths et al teach site specific attachment of PEG to thiols in an antigen binding fragment outside the variable region (see column 3 and 4) and the antigen binding fragment is a Fab or Fab' (see column 2, lines 46-58) and the antibody fragment has an effector attached (see abstract) and compositions comprising such.

Hence, the instant claims are rejected under 35 U.S.C. 102(e) as being anticipated by Griffiths et al.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pedley et al (Br. J. Cancer. 1994. 70:1126-1130; IDS – 12/13/2004) in view of Goodson et al (BioTechnology. 1990. 8:343-346; IDS – 12/13/2004) and in view of Woghiren et al (Bioconjugate Chem. 1993. 4:314-318; IDS – 12/13/2004)

The claims have bee described supra. In addition, claim 5 is drawn to an antibody fragment according to claim 4 wherein the polymer is methoxy(polyethylene glycol) and derivatives thereof.

Pedley et al has been described supra.

Goodson et al teach a modified protein with the addition of methoxy(polyehtylene glycol) to cysteine residues in the protein (see abstract, in particular).

Woghiren et al also teach a modified protein with the addition of methoxy(polyehtylene glycol) to cysteine residues in the protein, in addition to teaching the preparation of a new activated form of PEG that is a stable reagent, but readily reacts with the thiol group of cysteine to form a disulfide-linked PEG aduct.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the invention as claimed by combining the studies of Pedley et al, Goodson et al and Woghiren et al as described below, and have used the methoxy(polyethylene glycol) of Goodson et al in the method of Pedley et al to produce a polymer-modified antigen binding fragment.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the teachings of Pedley et al because Pedley et al teach the covalent attachment of polytethylene glycol) (PEG) to an antibody, a Fab fragment, and a Fab' fragment of anti-CEA (see abstract). Pedley

modified the cysteine residues outside the variable region of the antibody fragments with PEG producing two polymer molecules per antibody (see page 1128, right side first paragraph). Pedley et al also teach the radiolabeling of the PEG-modified antibodies (see page 1127, left column, Radiolabeling) and the P/G-modified antibody fragment in PBS (see page 1127 left column first Pedley et al modified 111 paragraph). Since claim 5 recites the polymer is methoxytpolyethylene glycol) and derivatives thereof, the claim is being interpreted as reading on polytethylene glycol).

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the teachings of Pedley et al with Goodson et al and Woghiren et al because Goodson et al teach a modified protein with the addition of methoxy(polyehtylene glycol) to cysteine residues in the protein and Woghiren et al also teach a modified protein with the addition of methoxy(polyehtylene glycol) to cysteine residues in the protein, in addition to teaching the preparation of a new activated form of PEG that is a stable reagent, but readily reacts with the thiol group of cysteine to form a disulfide-linked PEG aduct.

Thus, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have to used the methoxy(polyethylene glycol) of Goodson et al in the method of Pedley et al to produce a polymer-modified antigen binding fragment because Goodson et al teach "This method has general applicability for modifying any therapeutic protein at a specific site and thereby altering its potency" (see abstract). In addition, one of ordinary skill in the art would have been motivated to used the methoxytpolyethylene glycol) of Goodson et al in the method of

Pedley et al to produce a polymer-modified antigen binding fragment because Woghiren et al teach "we have prepared a new activated form of PEG that is a stable reagent, but readily reacts with the thiol group of cysteine to fonn a disulfide-linked PEG aduct." (See introduction). In addition, one of ordinary skill in the art would conclude that many chemically altered PEG molecules could be used t produce a polymer-modified antigen binding fragment.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Please note that all of the following references are included in the Information Disclosure Form submitted by the applicant on 12/13/2004.

1. Zapata et al. FASEB J. 1995. 9:A1479.
2. Zapata et al. U.S. Patent 6,214,984, Continuation Date 04/20/1995.
3. Jacobs et al. U.S. Patent 5,853,723; Date Filed 09/20/1996.
4. Bodmer et al. WO 89/01974; International Publication Date 03/09/1989.
5. Faanes et al. U.S. Patent 5,695,760, Date Filed 04/1995.

Conclusion

11. No claims are allowed

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER